

What is claimed is:

1. A method for modulating the activity of a calcium channel in a pre-determined region of a tissue or organ of a mammal, the method comprising:
 - a) contacting the region with a nucleic acid encoding a GEM protein or a variant thereof, the contacting being under conditions sufficient to express the GEM protein or variant within the region; and
 - b) expressing the GEM protein or variant at a level sufficient to modulate the activity of the calcium channel.
2. The method of claim 1, wherein the region of the tissue or organ is associated with a specific biological function.
3. The method of claim 1 or 2, wherein the region of the tissue or organ has a specific anatomical designation.
4. The method of claim 1, wherein the pre-determined region is within the heart, central nervous system (CNS), or vasculature.
5. The method of claim 1, wherein the pre-determined region comprises cardiac or smooth muscle.
6. The method of claim 1, wherein the method further comprises inhibiting L-type calcium current ($I_{Ca,L}$) by at least about 10% as determined by a standard electrophysiological assay.
7. The method of claim 6, wherein the method further comprises reducing the number of L-type calcium current channels by at least about 10%.
8. The method of claim 1, wherein the method further comprises administering to the mammal at least one vascular permeability agent.

9. The method of claim 8, wherein the vascular permeability agent is administered before step a) of the method.
- 5 10. The method of claim 1 or 9, wherein the vascular permeability agent is administered after step a) of the method.
11. The method of claim 8, wherein the vascular permeability agent is perfused through the tissue or organ region at a rate of between about 0.5 ml/min to about 100
10 ml/min.
12. The method of claim 10, wherein the vascular permeability agent is perfused through the region for between about 10 seconds to about five hours.
- 15 13. The method of claim 8, wherein the vascular permeability agent comprises a solution having less than about 500 micomolar of a calcium salt.
14. The method of claim 13, wherein the vascular permeability agent comprises a solution having less than about 100 micomolar of a calcium salt.
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15. The method of claim 8, wherein the method comprising administering at least one of VEGF165 and nitroglycerin to the tissue or organ region prior to step a).
16. The method of claim 15, wherein the nucleic acid is a recombinant animal virus
25 that encodes the Gem protein or variant and the method further comprises administering between from about 10^7 to about 10^{12} plaque forming units (p.f.u.) of the recombinant animal virus to the mammal.
17. The method of claim 15, wherein the method further comprises administering at
30 least one of VEGF165 and nitroglycerin to the tissue or organ region after step a).

18. The method of claim 1, wherein the method further comprises administering to the mammal at least one standard calcium channel blocker.

19. The method of claim 18, wherein the standard calcium channel blocker is administered before, during or after step (a) of the method.

20. The method of claim 1, wherein the recombinant animal virus is a DNA virus.

21. The method of claim 20, wherein the DNA virus is a recombinant adenovirus.

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22. The method of claim 21, wherein the recombinant adenovirus comprises nucleic acid sequence comprising as operably linked components: i) a sequence encoding the GEM protein or variant thereof; ii) at least one nucleic acid sequence adapted to facilitate site-specific DNA recombination using a recombinase and iii) at least one nucleic acid sequence providing an essential adenovirus function.

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23. The method of claim 22, wherein the recombinase is Cre or Flp.

24. The method of claim 22, wherein the recombinant adenovirus further comprises the following nucleic acid sequences as operably linked components: i) a first inverted terminal repeat sequence (ITR), ii) a first lox P site, iii) an adenovirus packaging sequence (ψ), iv) a strong viral promoter, v) sequence encoding the GEM protein or variant, v) a polyadenylation signal (An), vi) a second lox P site; and vii) a second inverted repeat sequence (ITR).

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25. The method of claim 24, wherein the recombinant adenovirus further comprises an internal ribosome entry site (IRES).

26. The method of claim 25, wherein the recombinant adenovirus further comprises at least one adenovirus early gene (E2 and E4) or a functional fragment thereof.

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27. The method of claim 26, wherein the recombinant adenovirus further comprises sequence encoding a selectable marker.
28. The method of claim 27, wherein the selectable marker is an in-frame fusion
5 encoding a fluorescent, phosphorescent or chemiluminescent protein.
29. The method of claim 22, wherein the recombinant adenovirus further comprises the following operably linked components in sequence: i) a first inverted terminal repeat sequence (ITR), ii) a first lox P site, iii) a packaging site (ψ), iv) a cytomeglovirus
10 promoter, v) sequence encoding the GEM protein or variant, vi) an internal ribosome entry site (IRES), vii) a polyadenylation signal (A_n), viii) a second lox P site; ix) a sequence encoding the adenovirus early region 2 and early region 4 genes; and x) a second inverted repeat sequence (ITR).
- 15 30. ~~The method of claim 29, wherein the recombinant adenovirus has a molecular weight between about 35 kilobases to about 40 kilobases.~~ *weight?*
31. The method of claim 21, wherein the recombinant adenovirus is administered to the mammal at a titre of between about 10^8 to 10^{12} p.f.u.
- 20 32. The method of claim 1, wherein expression of the GEM protein or variant encoded by the recombinant animal virus can be detected in the region from at least about 12 hours after the contact as determined by a standard Gem protein detection assay.
- 25 33. The method of claim 32, wherein the expression of the GEM protein or variant is sufficient to modulate the activity of an L-type calcium channel from at least about 24 hours after contact with the virus as determined by a standard electrophysiological assay.
- 30 34. The method of claim 32, wherein the expression of the GEM protein or variant is sufficient to modulate the activity of the L-type calcium channel from between about 24

hours to about one (1) month after the contact with the virus as determined by the standard electrophysiological assay.

35. The method of claim 1, wherein the GEM protein encoded by the recombinant animal virus is identical to the human GEM protein sequence shown as SEQ ID NO. 1.

36. The method of claim 1, wherein the GEM variant encoded by the recombinant animal virus is at least 70 % identical to the protein sequence shown as SEQ ID NO. 1.

37. The method of claim 36, wherein the GEM variant encoded by the recombinant animal virus has a C- or N-terminal deletion of between from about 1 to about 100 amino acids.

38. The method of claim 37, wherein the affinity of the GEM variant for calmodulin is reduced by at least 50% as determined by a standard calmodulin binding assay.

39. The method of claim 38, wherein the variant encoded by the recombinant virus has a single amino acid change from the protein sequence shown as SEQ ID NO. 1.

40. The method of claim 19, wherein the single amino acid change is at position 269 (W269G) of the GEM protein sequence.

41. The method of claim 1, wherein the pre-determined region is within a ventricular or atrial chamber of the heart.

42. The method of claim 41, wherein the pre-determined region is further defined as the atrioventricular (AV) node, sinoatrial (SA) node, or the Purkinje fibers (Bundle of His).

43. The method of claim 40, wherein the L-type calcium channel activity is reduced in at least one of the AV and SA nodes and the method further comprises shortening the

action potential duration (APD) by at least about 25% as measured by the APD₅₀ or APD₉₀.

44. The method of claim 43, wherein the level of expression of the GEM protein or variant is not sufficient to change the resting membrane potential of the L-type calcium channel detectably.

45. The method of claim 43, wherein the level of expression of the GEM protein or variant is not sufficient to change the phase 2 depolarization of action potential detectably.

10 46. The method of claim 41, wherein the L-type calcium channel activity is reduced in a pre-determined region of an atrium and the method further comprises shortening the QT interval by at least about 10% as determined by a standard electrophysiological assay.

15 47. The method of claim 41, wherein the L-type calcium channel activity is reduced in a pre-determined region of an atrium and the method further comprises prolonging at least one of the PR interval or AH interval of the heart by at least about 10% as determined by a standard electrophysiological assay.

20 48. The method of claim 47, wherein the level of expression of the GEM protein or variant is not sufficient to prolong the HV interval of the heart detectably.

49. A method for preventing or treating a medical condition associated with undesired calcium channel activity, the method comprising:

- 25 a) contacting a pre-determined region of a tissue or organ with a nucleic acid encoding a GEM protein or a variant thereof, wherein the contacting is under conditions sufficient to express the GEM protein or variant in the region,
- b) expressing the GEM protein or variant under conditions suitable to
- 30 modulate the activity of the calcium channel; and

c) modulating the activity of the calcium channel sufficient to prevent or treat the medical condition.

50. The method of claim 49, wherein the medical condition is associated with impaired heart function.

51. The method of claim 49, wherein the method further comprises directly administering the nucleic acid to at least one of the atrioventricular (AV) node or the sinoatrial (SA) node.

52. The method of claim 50, wherein the impaired heart function is arrhythmia, fibrillation, hypertrophic cardiomyopathy, or hypertrophic obstructive cardiomyopathy.

53. The method of claim 52, wherein the cardiac arrhythmia is atrial fibrillation.

54. The method of claim 50, wherein the recombinant animal virus encodes a Gem variant and the impaired heart function is one or more of cardiac hypertrophy.

55. The method of claim 50, wherein the recombinant animal virus encodes a Gem variant and the impaired heart function is one or more of cardiac hypertrophy. fibrosis.

56. The method of claim 50, wherein the nucleic acid encodes a Gem variant and the impaired heart function is one or more of cardiac remodeling.

57. The method of any one of claims 54-56, wherein the encoded Gem variant includes a mutation at position 269 of the wild-type Gem protein.

58. The method of claim 57, wherein the Gem variant includes a W269G mutation.

59. The method of claim 49, wherein the method further comprises administration of at least one calcium channel blocker.
60. The method of claim 59, wherein the administration of the calcium channel
5 blocker is before or after step (a) of the method.
61. The method of claim 49, wherein the method further comprises administering a standard AV nodal blocking agent.
- 10 62. The method of claim 49, wherein the nucleic acid is a recombinant animal virus that encodes the Gem protein or variant.
63. A therapeutic system or kit for modulating the activity of an L-type calcium channel in a pre-determined region of a tissue or organ of a mammal, the system
15 comprising:
 (a) a composition comprising a nucleic acid encoding a mammalian Gem protein or variant,
 (b) at least one permeability agent; and optionally
 (c) an implementation adapted to administer the composition and the
20 permeability agent to the pre-determined region of the tissue or organ of the mammal.
64. The method of claim 63, wherein the nucleic acid sequence is part of a recombinant animal virus comprising as operably linked components: i)
25 sequence encoding the mammalian GEM protein or variant thereof; ii) at least one nucleic acid sequence adapted to facilitate site-specific DNA recombination; and iii) at least one nucleic acid sequence providing an essential adenovirus function.
65. The therapeutic system of claim 63, wherein the implementation is an injection
30 needle, stent or catheter device operably linked to a pump.

66. The therapeutic system of claim 63; wherein the composition further comprises a physiologically acceptable carrier.
67. The therapeutic system of claim 63, wherein the permeability agent is one of serotonin, bradykinin, platelet-activating factor, prostaglandin E₁, histamine, vascular endothelium growth factor (VEGF), zona occludens toxin, interleukin-2, plasma kinins; or a functional fragment thereof.
68. The therapeutic system of claim 63, wherein the permeability agent is at least one of VEGF165 and nitroglycerin.
69. The therapeutic system of claim 63, wherein the permeability agent is L-N-monomethyl arginine, L-N-nitro-arginine methyl ester, or 8-Br-cGMP.
70. The therapeutic system of claim 63, wherein the permeability agent is a vasodilator.
71. The therapeutic system of claim 70, wherein the vasodilator is angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist, a nitrovasodilator, phosphodiesterase inhibitor, direct vasodilator, adrenergic receptor antagonist, calcium channel blocking agent, or a sympathomimetic.
72. The therapeutic system of claim 70, wherein the nitrovasodilator is nitroglycerin.
73. The therapeutic system of claim 62 in which one or more of (a) and (b) further comprises a physiologically acceptable carrier.
74. The therapeutic system of claim 63, wherein the vascular permeability agent is a solution having a less than about 500 μ moles/L of a calcium salt.

75. The therapeutic system of claim 74, wherein the vascular permeability agent is a solution having a less than about 100 $\mu\text{moles/L}$ of a calcium salt.